# Transplant Immunology I
## Developing the Immune Response to the Renal Allograft
## or
## (There is no evolutionary pressure to permit transplantation…)

C.M. Yuan

# Specific Aims

- To describe the physiology of the recipient immune response to the renal allograft.
- To understand how immunosuppressives currently in use are thought to prevent rejection based on immune physiology.

# Questions??

At the end of this lecture, you should be able to answer the following questions…

1. What is the result of TCR-peptide-MHC recognition not accompanied by costimulation?
2. Does the initial immune response to the allograft involve interaction with “self” or “donor” HLA?
3. True or false? HLA Class II can be expressed by endothelial cells.

# Kidney Transplantation
## A Time-line

- 1902 Albert, auto-transplantation of a dog kidney.
- 1905 Carrel, autografts/allografts in dogs and cats failed after brief function.
- 1909 Unger, xenograft (monkey to human)--no urine produced.
- 1914 Carrel

  “All our efforts must now be directed toward the biological methods which will prevent the reaction of the organism against foreign tissue and allow the adapting of homoplastic grafts to their hosts.”

# Kidney Transplantation
## A Time-line

- 1953 Simonson/Dempster, mechanism of renal allograft rejection in the dog. Pelvic position of allograft. Rejection--an immunologic process--probably humoral.
- 1954 Murray, transplant between monozygotic twins.
- 1955 Hume, reported 9 renal allograft transplants in humans.
- 1960 Calne/Kuss, 6-mercaptopurine.
- 1962 Hamberger/Terasaki, tissue typing.
- 1966 Kussmeyer/Nielson, crossmatch between donor cells and recipient serum.

# Kidney Transplantation
## A Time-line

- 1970's HLA typing introduced.
- 1973 Opelz, transfusion effect described.
- 1978 CyA introduced. HLA-DR typing introduced.
- 1981 Cosimi, et al; OKT3 introduced for acute rejection.
- 1989 FK506 introduced.
- 1993 Mycophenolate mofetil introduced.
- ???? Xenografts?

  Specific Tolerance via manipulation of co-stimulation?

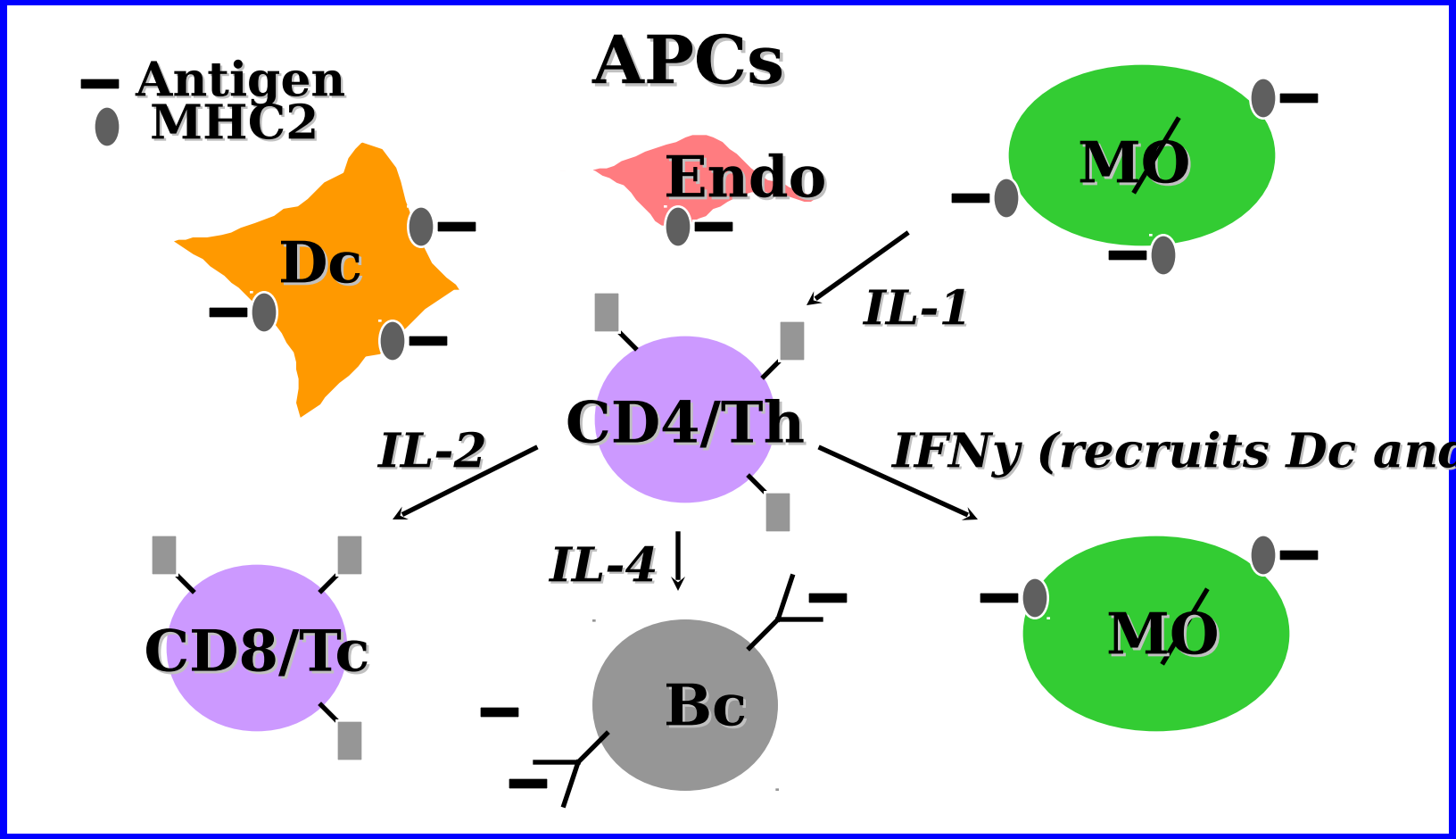
# Immune Recognition

a) Unresponsiveness to all “self” antigens, i.e. tolerance.

b) Recognition of “non-self” antigens (tumors, pathogens, allografts*), with subsequent elimination.

*ALLOGRAFT RESPONSE IS STRONGER ($10^2$X) AND INVOLVES MORE LYMPHOCYTE RECRUITMENT.

# The Immune Response to an Antigen



# Immune Response to the Allograft Afferent Limb

a) MHC--Class I and II.

b) Minor Histocompatibility Antigens--H-Y antigen, HA-2 antigen (derived from myosin) or mitochondrial antigens (present in cleft as peptides).

c) Antigen processing and presentation--by professional and IFNy-stimulated APCs.

d) TCR--CD4 (helper) and CD8 (cytotoxic) cells.

e) Accessory Molecules--CD3, CD4/8, ICAM/LFA.

f) Costimulatory Antigens--B7 (APC), CD28 (Tcell).

g) Inhibitory Antigens--CTLA4

h) Second Messenger Systems--Protein tyrosine kinases, $Ca^{2+}$ mobilization, IP3/PKC, calcineurin, others.

i) Site of sensitization--peripheral or central.

j) Privileged sites--cornea, brain, testes, cartilege.

# The Major Histocompatibility Complex (MHC)

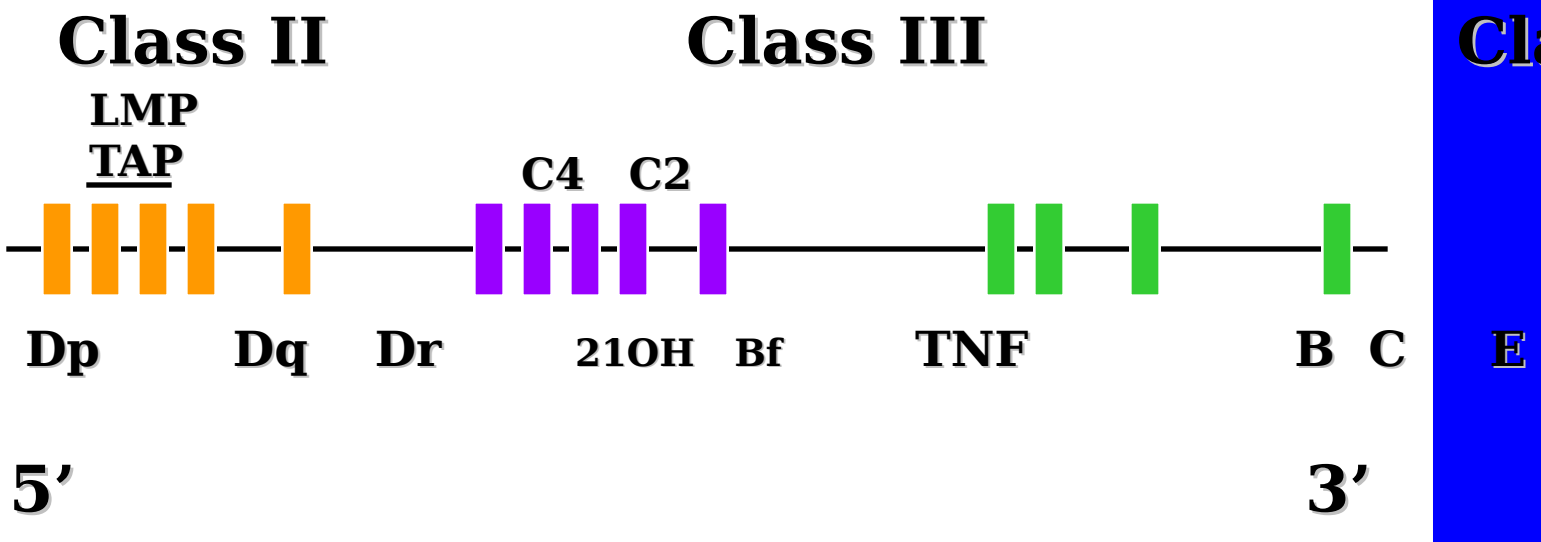
**DEFINITION:** The locus that encodes the cell surface glycoproteins primarily responsible for allograft rejection. In humans--the HLA.

"One of the most notable aspects of the MHC, and one of the most frustrating for the transplant surgeon, is the high degree of polymorphism…in the antigens that it encodes."

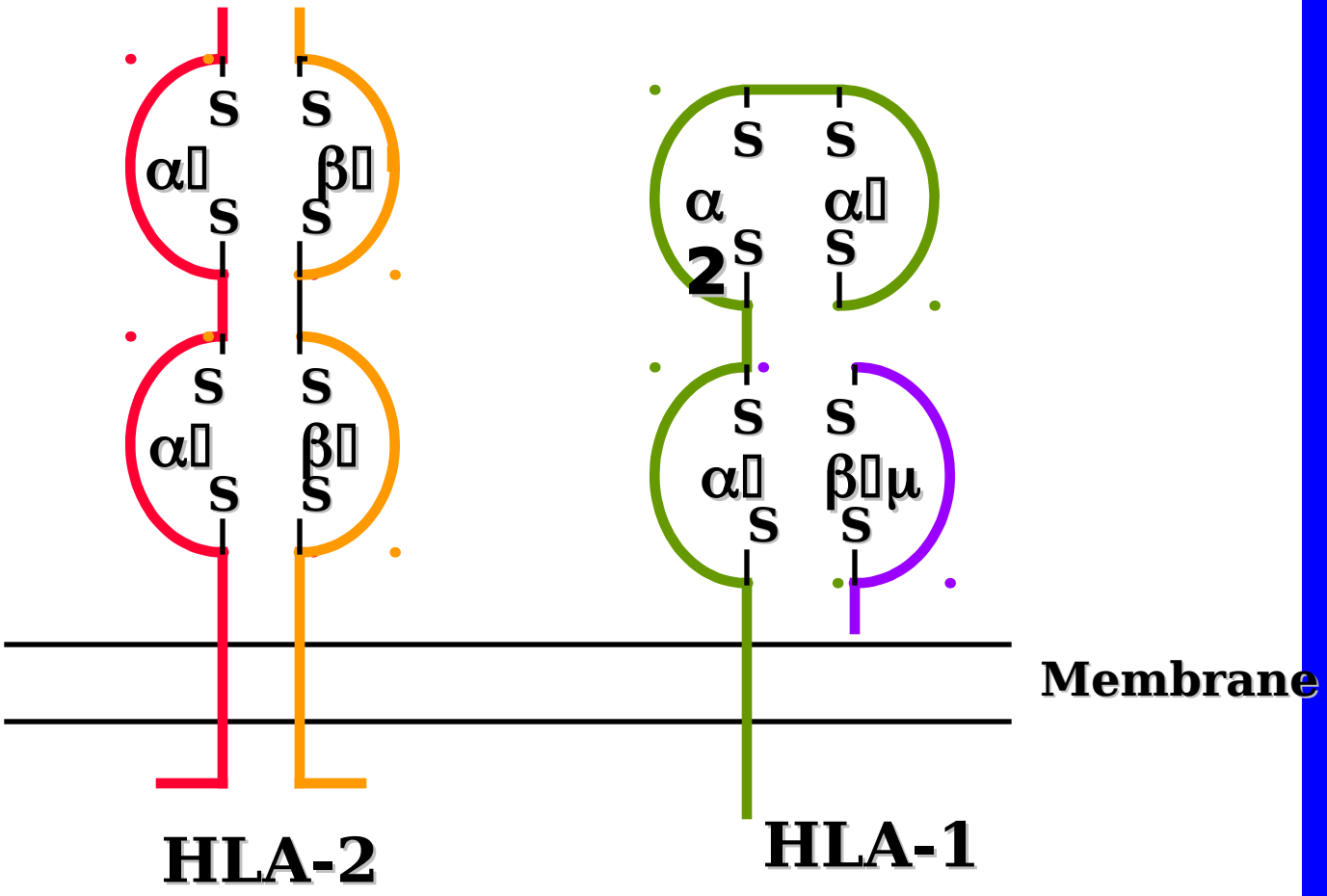
Dallman and Morris, 1994

This polymorphism is likely to have proved frustrating for pathogens as well…..

# The MHC Locus



# MHC Class I and II



# Comparing MHC Class I and II

| Properties | Class I | Class II |
| --- | --- | --- |
| ANTIGENS | HLA-A, B, C | HLA-D-DR/Q/P |
| TISSUE DISTRIBUTION | On virtually all cells | B-cell, dendritic cell, macrophage |
| FUNCTIONS | Endogenous Ag presented to CD8 (cytotoxic) T-cells | Exogenous Ag presented to CD4 (T-helpers) |

# Non-Polymorphic Molecules Involved in Antigen Presentation

Class 1-Like

a) encoded in the MHC.

b) HLA-E, -F, and -G.

c) ? involved in presentation of peptides specific to certain pathogens. HLA-G is expressed on the trophoblast, and may contribute to “tolerance” of mother to fetus.

Class II-Like

a) encoded in MHC

b) DMA/DMB--heterodimers necessary to peptide placement in HLA-II molecules.

Class III-Like

a) C2, C4, and Bf complement proteins

b) 21-OH hydroxylase

c) TNF alpha and beta

Others

a) TAP 1 and 2--transport of peptides into the Golgi for association with HLA-1 molecules.

b) Hsp70--mediates folding and degradation of denatured proteins.

c) LMP 2, LMP7--components of the proteosome, which processes endogenous proteins into peptide fragments.

# Non-Polymorphic Molecules (Outside the HLA) Involved in Antigen Presentation

CD1

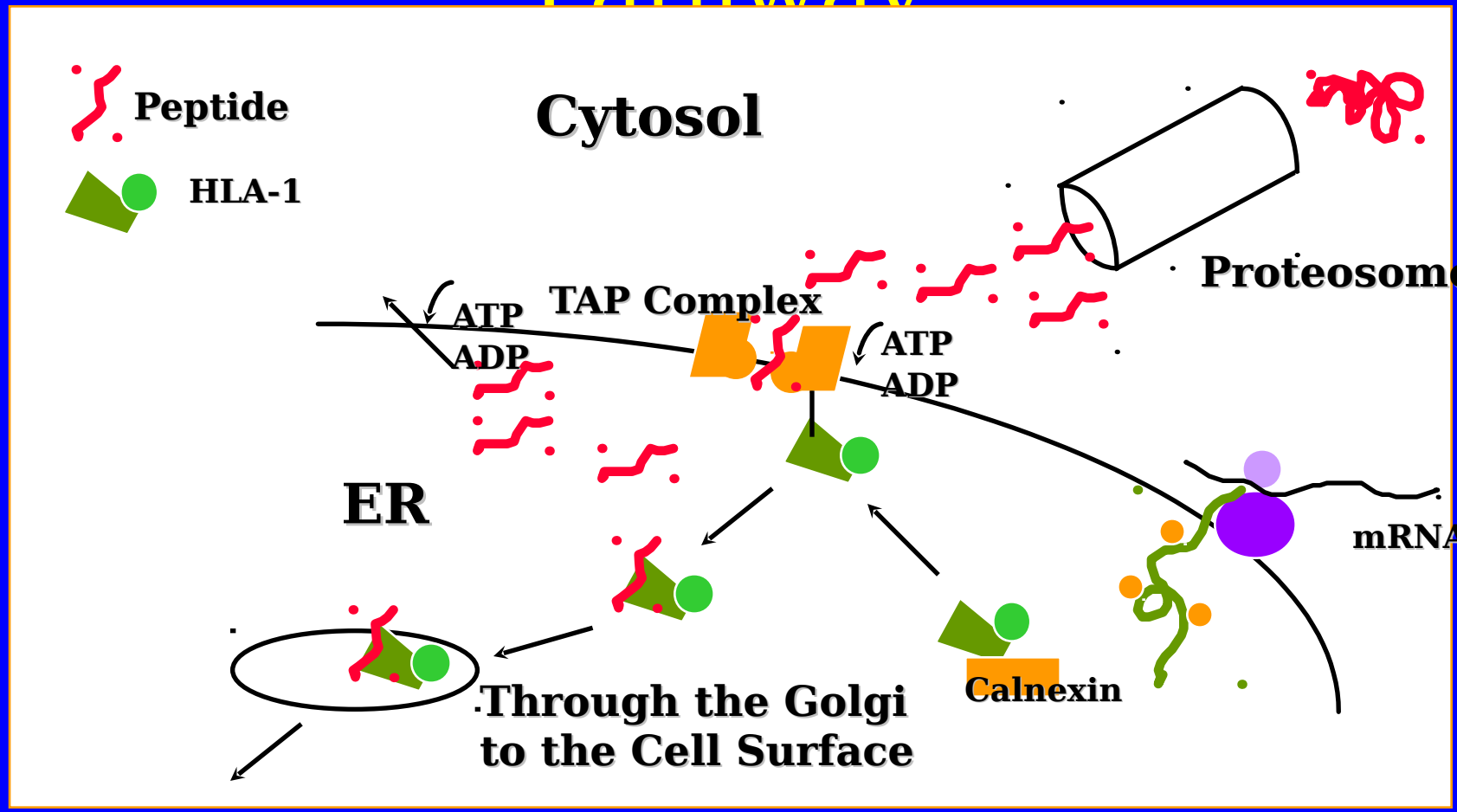
a) encoded outside the MHC

b) 5 non-polymorphic genes

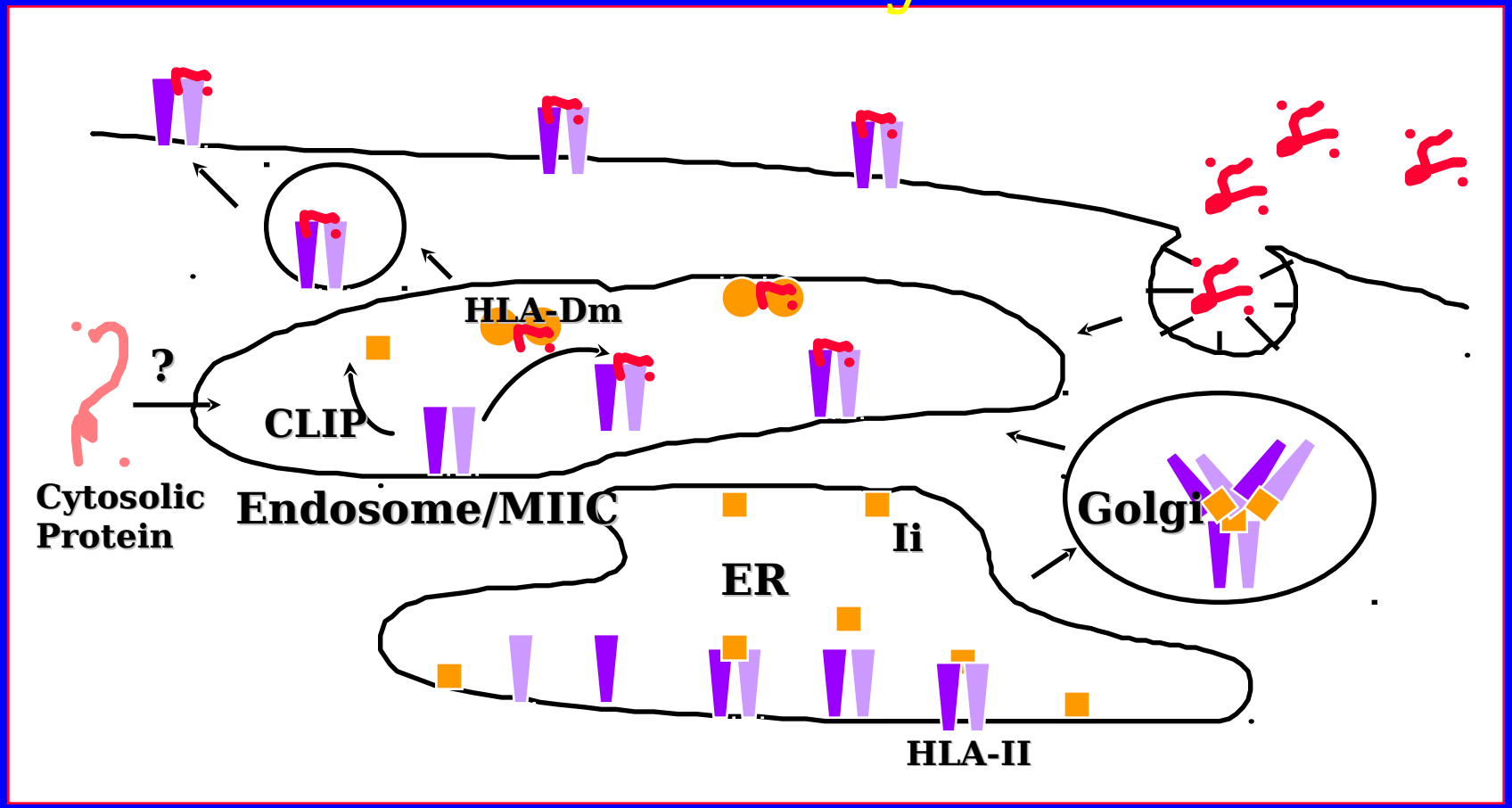
c) protein product associated with beta-2 microglobulin

d) appears to present lipid and glycolipid residues, rather than peptide, and are recognized by specific TCRs.

# Synthesis and Assembly of HLA-1 Complex/Endogenous Pathway



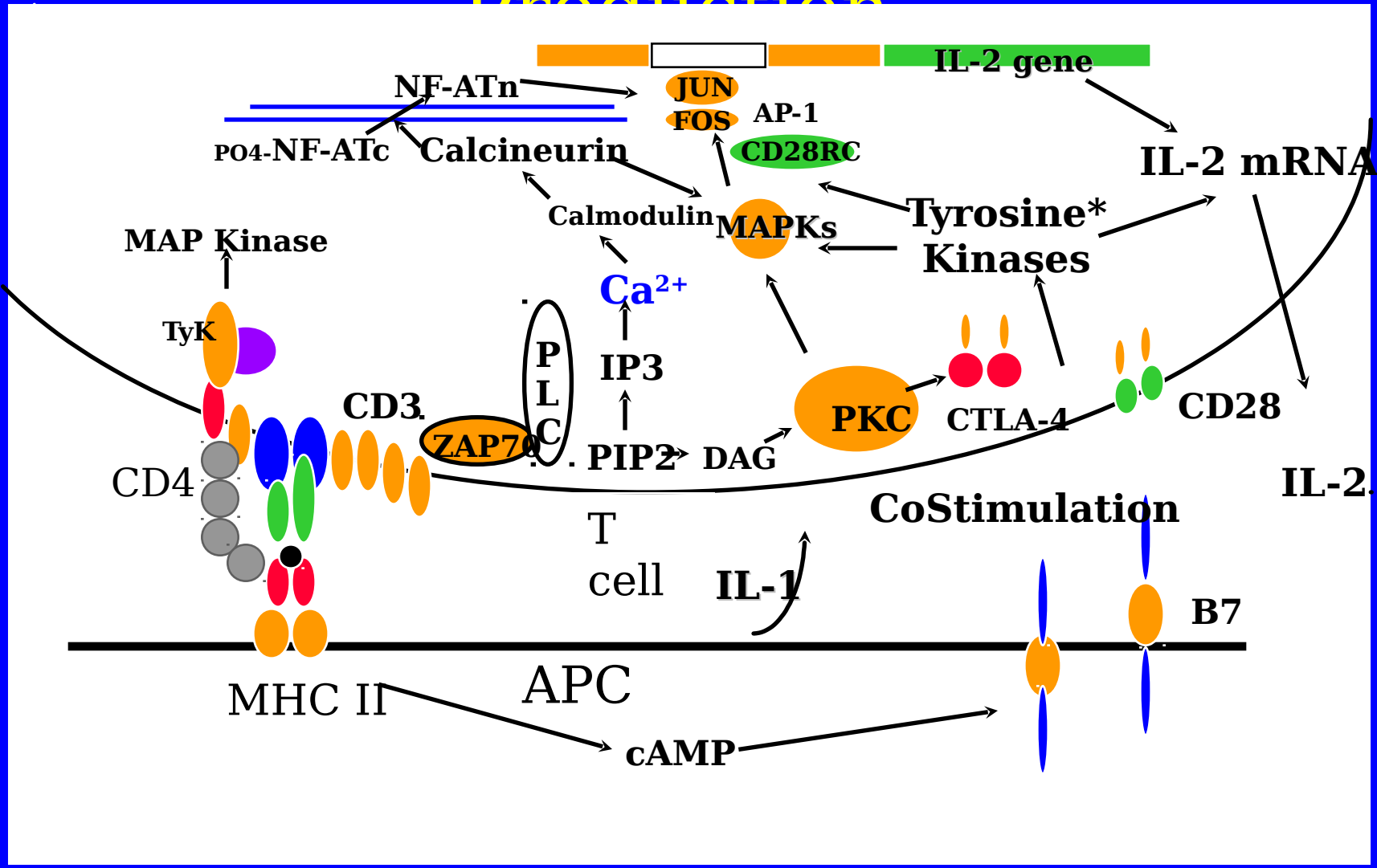
# Synthesis and Assembly of HLA-II Complex/Exogenous Pathway



# Rejection of the Allograft What is the Alloantigen?

- In allogeneic transplant the immediate “direct” immune response is most likely due to T-cell recognition of non-self HLA-I and HLA-II presented on donor APCs (dendritic cells/endothelia).
- Early in life, T- cells with reactivity to self HLA that is too weak or too strong are deleted by apoptosis in the thymus.
- After transplant, T-cells encounter “new” HLA molecules +/- “new” peptides for which they have a high affinity.
- Donor HLA/alloantigen may also be presented (later in the response) as peptide fragments presented on “self” HLA by “self” APCs-- “indirect allorecognition”. This pathway may play a greater role in chronic rejection.

# T Cell Activation Costimulation for IL-2 Production



# Costimulation

The concept (proposed originally by Bretscher and Cohn) that an antigen-specific lymphocyte immune response requires at least 2 stimuli from the APC. If the second stimulus (costimulation)--does not occur, tolerance ensues. At present, the two signals appear to be:

1. TCR-peptide-MHC recognition (Specific response)
2. T-cell ligand (CD28 “on” and/or CTLA4 “off”)-B7-1 or -2 binding (non-specific costimulation provides + or - “support”)

CD28/B7 may not be the only “co-stimulator” pair. In addition, other cell-cell interactions (as between ICAM-LFA) are also important.

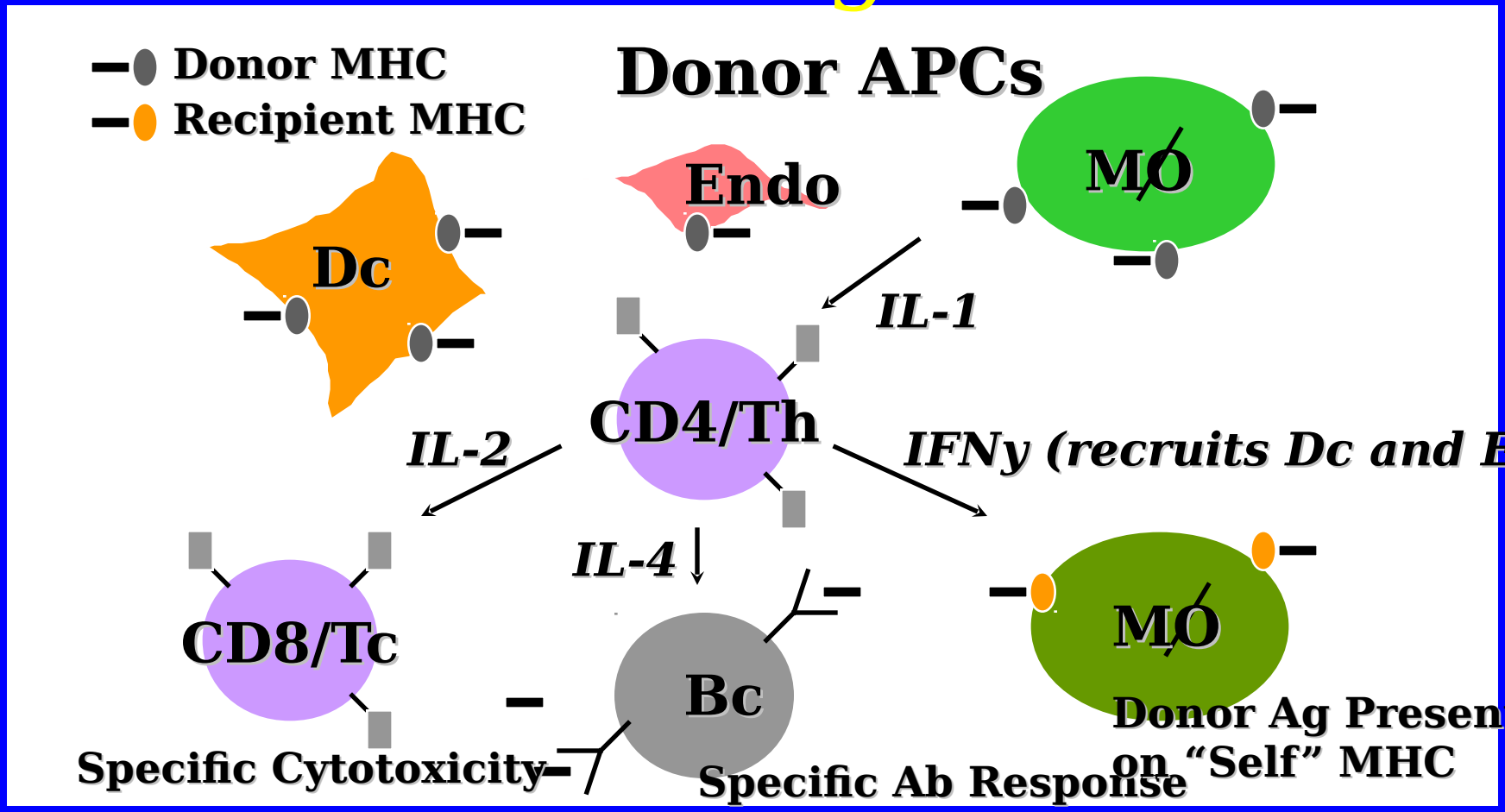
# Costimulation: Importance of Topography and Time

- Costimulation occurs in space--ie, the interaction between the surface molecules on the T-cell and the APC, with the activation of appropriate second messengers
- Costimulation also occurs over time--and timing of events, or their sequence, may also impact on whether an immune response occurs or tolerance develops.

So…The allograft has been recognized as non-self…

What happens next?

# The Immune Response to the Allograft



# Immune Response to the Allograft Effector Limb

**a) Humoral**

1. Cytokines: IL-1, IL-2, IL-4/5, $\gamma$-IFN
2. Antibody dependent, cell-mediated cytotoxicity
3. Complement dependent, cell-mediated cytotoxicity

**b) Cellular**

1. Cytotoxic T cells--CD8 (specific)
2. Natural killer cells--non-specific
3. Activated macrophages--non-specific

# Principal Cytokines Involved in Allograft Rejection

IL-1: produced by APCs, soluble costimulator of T-cell activation.

IL-2: produced by T-cells. T-cell growth factor, and stimulates production of other cytokines ($\gamma$IFN).

IL4/IL5: produced by T-cells. Stimulates B-cells.

$\gamma$-IFN: produced by T-cells. Induces MHCII production on endothelial and dendritic cells, and activates macrophages.

TNF$\alpha$: Produced by T-cells and macrophages. Cytotoxic, induces MHCI, pro-inflammatory.

# Cells Mediating Allograft Rejection

Role of CD4 (helper) vs. CD8 (cytotoxic) T-cells in the hierarchy of rejection…

First-set rejection:

Dependent on MHCII (and thus CD4 cells), as well as on cytokine production (IL-2, $\gamma$IFN). CD8 cells act secondarily--and depend on “help”

Second-set rejection:

CD8 “memory” is present, with less dependence on CD4 cell “help”.

# Stopping Rejection
# A Rationale

Based on a physiologic framework--how does one prevent/stop rejection?

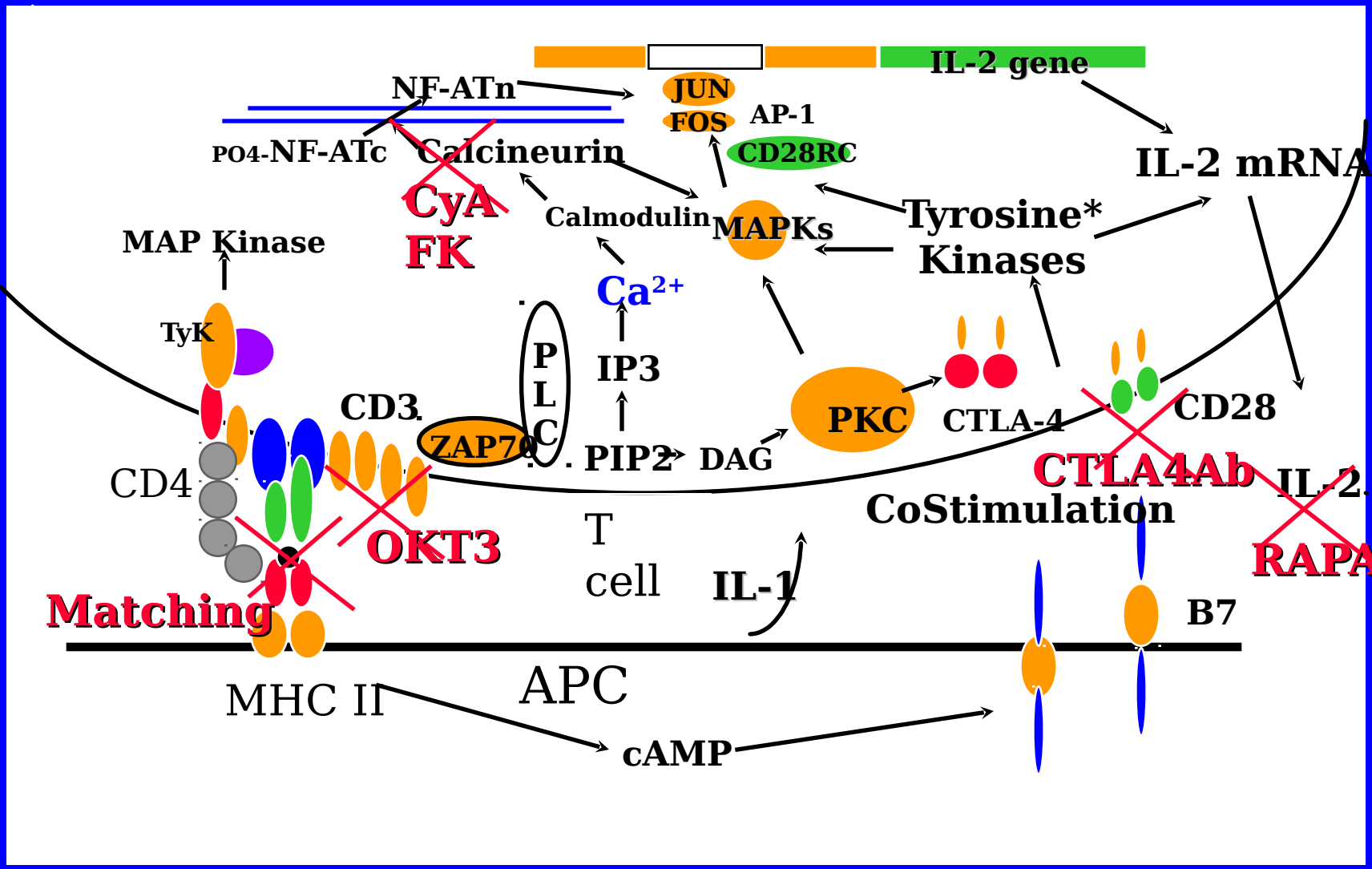
Proximal approach (ie, prevent specific immune response):

- Remove all T/CD3-cells (***ATG, OKT3***)
- Prevent recognition of the alloantigen by TCR (***Matching!***)
- Prevent costimulation--induce tolerance (***CTLA4Ab***)

Distal approach (ie, prevent non-specific immune response):

- Inhibit IL-2 production (***CyA, FK506***)
- Inhibit IL-2 action (***Rapamycin***)
- Inhibit T-cell proliferation (***Imuran, Mycophenolate***)
- Inhibit Inflammation (***Corticosteriods***)

# Where Do the Drugs Work?



And now you are ready to read about the clinical aspects of allograft matching and rejection... and to think about pigs... and the problems of xenografts...

# Answers!!

1. Induction of anergy or tolerance occurs in the absence of costimulation after TCR-MHC mediated antigen recognition .
2. Probably the intitial response to the allograft is directed against “donor” HLA .
3. HLA Class II can be expressed by endothelial cells stimulated by γIFN.